**PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

First Named Inventor: DODDA MOHAN RAO

Serial No: 10/524,478 Group Art Unit: 1626

Filed: 02-11-2005 Examiner: LOEWE, SUN JAE Y

Att. Docket No.: S2096/20001 Confirmation No.: 6950

For: NOVEL CRYSTALLINE FORM OF LINEZOLID

**REQUEST FOR DECLARATION OF AN INTERFERENCE WITH AN APPLICATION UNDER 37 CFR 41.202**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant requests that an interference be declared between this Application (the '478 Application) assigned to SYMED LABS LIMITED, and U.S. Patent Application No. 11/171,098 (the '098 Application) assigned to TEVA PHARMACEUTICALS, INC.

Applicant hereby makes the showing required under 37 C.F.R. 41.202(a)(l) though (a)(6).

**CERTIFICATE OF MAILING/TRANSMISSION PURSUANT TO 37 CFR 1.8**
I hereby certify that this correspondence and any attachments referenced therein is/are being mailed/transmitted to the USPTO by: (A) first class U.S. mail with sufficient postage (37 CFR § 1.1(a)); (B) facsimile (37 CFR § 1.6 (d)); or (C) EFS-Web (37 CFR § 1.6(a)(4)) on the date shown below.

Date: 6/4/2009 Signature: _____

Name: Joseph F. Murphy

Pursuant to 37 CFR 41.202(a), Applicant may suggest an interference with an Application. The suggestion must (37 CFR 41.202(a)(1) to (a)(6)):

(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,

(2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,

(3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),

(4) Explain in detail why the applicant will prevail on priority,

(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and

(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.

Applicant will now address each of the forgoing requirements.

**(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference**

Applicants respectfully request that an interference be declared between the above referenced United States Patent Application Serial No. 10/524,478 (the Symed '478 Application) assigned to SYMED LABS LIMITED, and U.S. Patent Application Serial No. 11/171,098 (the Teva '098 Application) assigned to TEVA PHARMACEUTICALS, INC.

The '478 application is a National Stage Entry of PCT/IN03/00336, filed October 16, 2003.

The '098 application claims Priority from:

U.S. Provisional Application No. 60/684,410, filed 05-24-2005 (Expired);

U.S. Provisional Application No. 60/678,440, filed 05-05-2005 (Expired);

U.S. Provisional Application No. 60/656,646, filed 02-24-2005 (Expired);

U.S. Provisional Application No. 60/656,778, filed 02-24-2005 (Expired);

U.S. Provisional Application No. 60/633,887, filed 12-07-2004 (Expired);

U.S. Provisional Application No. 60/602,227, filed 08-17-2004 (Expired);

U.S. Provisional Application No. 60/601,086, filed 08-12-2004 (Expired);

U.S. Provisional Application No. 60/584,283, filed 06-30-2004 (Expired);

U.S. Provisional Application No. 60/584,371, filed 06-29-2004 (Expired).

**(2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts**

**2.1 Identification of claims believed to interfere**

Claims 1 and 39 of the Symed '478 application are believed to interfere with claims 8-11, and 24-29 of the Teva '098 application.

**2.1 Proposal of one or more counts, and showing of how the claims correspond to the count**

Applicants suggest the proposed count identified below for the interference ("the Proposed Count"), and identify claims in the Symed '478 Application and the Teva '098 Application which correspond to the Proposed Count.

Proposed Count:

A crystalline linezolid characterized by:

(a) a powder X-ray diffraction pattern with peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 2l.1, 22.2, 25.4, 27.7, and 28.4 ± 0.2 degree 2 theta;

OR

(b) an FTIR spectrum with peaks at about 2817, 1335, 1229, 1200, and 662 cm-1, wherein there is at least a 99.8% enantiomeric excess of the linezolid form III.

**Claims of the Symed '478 Application which Correspond to the Proposed Count**

Claims 1 and 39 of the Symed '478 application correspond to part (a) of the proposed count. Because of the use of "or" correspondence to one part of the proposed Count is sufficient.

**Claims of the Teva '098 Application which Correspond to the Proposed Count**

Claims 8 and 9 of the Teva '098 application correspond exactly to parts (a) and (b) of the proposed count. Because of the use of "or" correspondence to one part of the proposed Count is sufficient.

Claims 10-11, and 24-29 correspond substantially to the Proposed Count because, for the reasons set forth more specifically hereinafter, these latter claims define the same patentable invention as the Proposed Count.

Claim 10 of the Teva '098 application depends from claim 9, and further specifies that the crystalline linezolid contains less than about 5% crystalline form II linezolid. The use of the specified percentage of crystalline form II does not specify a separate patentable invention. Accordingly, claim 10 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 11 of the Teva '098 application depends from claim 10, and further specifies that the crystalline linezolid contains less than about 0.5% crystalline form II. The use of the specified percentage of crystalline form II does not specify a separate patentable invention. Accordingly, claim 11 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 24 of the Teva '098 application depends from claim 1, and further specifies that the crystalline linezolid has a content of less than about 0.1% R-enantiomer of linezolid. The use of the specified percentage of the R-enantiomer of linezolid does not specify a separate patentable invention. Accordingly, claim 24 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 25 of the Teva '098 application depends from claim 1, and further specifies that the crystalline linezolid has a content of less than about 0.02% R-enantiomer of linezolid. The use of the specified percentage of the R-enantiomer of linezolid does not specify a separate patentable invention. Accordingly, claim 25 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 26 of the Teva '098 application depends from claim 9, and further specifies that the crystalline form II is characterized by a DSC thermogram substantially as shown in Figure 8. The use of the specified DSC thermogram of crystalline form II linezolid does not specify a separate patentable invention. Accordingly, claim 26 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 27 of the Teva '098 application correspond depends from claim 9, and further specifies that the crystalline form II linezolid is characterized by a DSC thermogram has an

endothermic peak around 155°C, an exothermic peak at around 160°C, and an endothermic peak at around 180°C. The use of the specified DSC thermogram data does not specify a separate patentable invention. Accordingly, claim 27 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 28 of the Teva '098 application corresponds depends from claim 9, and further specifies that the crystalline form II linezolid is characterized by FTIR peaks at 3364, 1748, 1675, 1537, 1517, 1445, 1410, 1401, 1358, 1329, 1287, 1274, 1253, 1237, 1221, 1145, 1130, 1123, 1116, 1078, 1066, 1049, 907, 852, and 758 $cm^{-1}$. The use of the specified FTIR data for crystalline form II does not specify a separate patentable invention. Accordingly, claim 28 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

Claim 29 of the Teva '098 application correspond depends from claim 9, and further specifies that the crystalline form II is characterized by FTRaman peaks at 2853, 1673, 1440, 1409, 1207, 651, 432, and 142 $cm^{-1}$. The use of the specified FTRaman peak data for crystalline form II linezolid does not specify a separate patentable invention. Accordingly, claim 29 corresponds substantially to the Proposed Count, and most particularly to parts (a) and (b) of the Proposed Count.

**(3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a)**

Rule 202(a)(3) requires the Applicants to provide a claim chart for each count showing at least one claim of each party and showing how the claims interfere. Applicants accordingly submit, attached hereto as Exhibit A, a claim chart which includes a copy of the Proposed Count, at least one claim from each of the Symed '478 Application and '098 Application which correspond to the Proposed Count, and an identification of why the claims interfere.

Pursuant to 37 C.F.R. 41.203(a), relating to interfering subject matter, an "[a]n interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party, and vice versa." A claim of one inventor can be said to interfere with the claim of another inventor if they each have a patentable claim to the same invention. The Office practice and the case law define

"same invention" to mean patentably indistinct inventions. Case v. CPC Int'l, Inc., 730 F.2d 745, 750, 221 USPQ 196, 200 (Fed. Cir. 1984); Aelony v. Arni, 547 F.2d 566, 570, 192 USPQ 486, 489-90 (CCPA 1977); Nitz v. Ehrenreich, 537 F.2d 539, 543, 190 USPQ 413, 416 (CCPA 1976); Ex parte Card, 1904 C.D. 383, 384-85 (Comm'r Pats. 1904). MPEP 2301.03. Here, the claims of the Symed '478 application are directed to the same invention as the claims of the Teva '098 application.

**3.1 The Interfering Subject Matter**

The claims of both applications are directed to a polymorphic form of linezolid (termed "form III" in the Symed '478 application, and "form IV" in the Teva '098 application), and define the "same invention", and thus "the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party, and vice versa".

The claims of both applications are directed to the same polymorphic form of linezolid based on the data used to characterize the claimed polymorphic form of linezolid.

**3.2 XRPD Data**

The linezolid polymorphic form of linezolid as claimed in the Symed '478 has an X-ray powder diffraction (XRPD) spectrum with peaks at 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees 2θ. The linezolid polymorphic form of linezolid as claimed in the Teva '098 has an XRPD spectrum with peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 21.1, 22.2, 25.4, 27.7, and 28.4 degrees 2θ. As set forth in the Second Declaration of Dr. Mohan Rao (submitted herewith), a comparison of these XRPD spectra clearly show the claims are directed to the same polymorphic form (see Second Declaration of Dr. Mohan Rao, at ¶14).

**3.3 Inherent Properties**

In addition, the further characteristics of the linezolid polymorphic form are inherently present in the polymorphic form as claimed in the Symed '478 application. The Court of Appeals for the Federal Circuit has stated that commonplace properties of a claimed invention may be deemed "inherent" to the invention, and that specific conception of these properties is not required (Hitzeman v. Rutter, 243 F.3d 1345, at 1354). For example, in a count directed to a new crystalline form of ampicillin that recited the compound's molecular weight, the CAFC held that it was sufficient to possess the claimed compound and to characterize it by water content and

infrared spectrograph, without demonstrating knowledge of the compound's molecular weight. See Silvestri v. Grant, 496 F.2d 593, 599, 181 USPQ 706, 709 (1974). In Silvestri, the CAFC held that it was not necessary to show that the inventors had actually determined the molecular weight of the ampicillin because this property "add[s] nothing to the count beyond that determined by the water content and infrared spectrograph." *Id.* This reasoning follows from the recognition that "attorneys often write compound claims including a statement of some inherent property, general or specific," and that "[w]here the balance of the claim fully identifies the compound ... and the property is inherent, we fail to see that such statements add anything to the claim definition of the named compound." (see Hitzeman v Rutter, at 1354, citing In re Ruschig, 52 C.C.P.A. 1238, 343 F.2d 965, 973 n. 8, 145 USPQ 274, 286 n. 8 (1965)).

To invoke the "inherent conception" rule of Silvestri, the inventor needs to show that the allegedly inherent property adds nothing to the count beyond the other recited limitations, and is redundant to the count. Silvestri, 496 F.2d at 599, 181 USPQ at 709. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); Abbott Labs v. Geneva Pharms., Inc., 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed characteristics."); Atlas Powder Co. v. Ireco, Inc., 190 F.3d 1342, 1348-49 (Fed. Cir. 1999) ("Because 'sufficient aeration' was inherent in the prior art, it is irrelevant that the prior art did not recognize the key aspect of [the] invention.... An inherent structure, composition, or function is not necessarily known.")>; SmithKline Beecham Corp. v. Apotex Corp., 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-

07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate). MPEP 2112.

Here, the inherent properties adds nothing to the count beyond the other recited limitations, is redundant to the count, and is necessarily present in the invention described by the count, and it would be so recognized by persons of ordinary skill in the art.

**3.4 FTIR**

The linezolid polymorphic form of linezolid as claimed in the Teva '098 application has an FTIR spectra with peaks at 2817, 1335, 1229, 1200, and 662 $cm^{-1}$. As set forth in the Second Declaration under 1.132 of Dr. Mohan Rao, the FTIR spectra for the linezolid polymorphic form as claimed in the Symed '478 application has an FTIR spectra with peaks at 2817, 1335, 1229, 1200, and 662 $cm^{-1}$. As set forth in the Second Declaration of Dr. Mohan Rao, a comparison of these FTIR spectra clearly shows the claims are directed to the same polymorphic form (see Second Declaration of Dr. Mohan Rao, at ¶19).

**3.5 DSC Thermogram**

The linezolid polymorphic form of linezolid as set forth in the Teva '098 application has an DSC thermogram with a peak at 179.07°C (see '098 application, Figure 3). As set forth in the Second Declaration under 1.132 of Dr. Mohan Rao, the DSC thermogram with a peak at 178.96°C. As set forth in the Second Declaration of Dr. Mohan Rao, a comparison of these DSC thermograms clearly show the claims are directed to the same polymorphic form (see Second Declaration of Dr. Mohan Rao, at ¶24).

**3.6 Summary**

Here, as can be seen in Exhibit A and the Second Declaration under 1.132 of Dr. Mohan Rao, the subject matter of the claims of the instant application would, if prior art, have anticipated or rendered obvious the subject matter of the claims of the '098 application, and vice versa, and thus the claims of the instant application and the '098 application are directed to interfering subject matter. The claims accordingly interfere within the meaning of 37 C.F.R. 41.203(a).

**(4) Explain in detail why the applicant will prevail on priority**

**4.1. Applicants have the earlier effective filing date and constructive reduction to practice date**

Applicants will prevail on priority because Applicants can show, with respect to the Proposed Count, an effective filing date and constructive reduction to practice date that is earlier than the corresponding dates of the Teva '098 Application.

In accordance with 35 U.S.C. 102(g)(1), a party involved in an interference proceeding under 35 U.S.C. 135 or 291 may establish a date of invention under 35 U.S.C. 104. With regards to an Invention made abroad, 35 U.S.C. 104 sets forth:

> (1) PROCEEDINGS.-In proceedings in the Patent and Trademark Office, in the courts, and before any other competent authority, an applicant for a patent, or a patentee, may not establish a date of invention by reference to knowledge or use thereof, or other activity with respect thereto, in a foreign country other than a NAFTA country or a WTO member country, except as provided in sections 119 and 365 of this title.
>
> (2) RIGHTS.-If an invention was made by a person, civil or military-
>
> (A) while domiciled in the United States, and serving in any other country in connection with operations by or on behalf of the United States,
>
> (B) while domiciled in a NAFTA country and serving in another country in connection with operations by or on behalf of that NAFTA country, or
>
> (C) while domiciled in a WTO member country and serving in another country in connection with operations by or on behalf of that WTO member country, that person shall be entitled to the same rights of priority in the United States with respect to such invention as if such invention had been made in the United States, that NAFTA country, or that WTO member country, as the case may be.

As set forth in 35 U.S.C. 104, as amended by GATT (Public Law 103-465, 108 Stat. 4809 (1994)) and NAFTA (Public Law 103-182, 107 Stat. 2057 (1993)), provides that an applicant can establish a date of invention in a NAFTA member country on or after December 8, 1993 or in WTO member country other than a NAFTA member country on or after January 1, 1996. (See MPEP 2138.02). Here, the invention was made in India, which is a member of the

WTO, and has been since January 1, 1995 (see Exhibit B, attached), and thus is entitled to a date of invention earlier than the effective filing date of the Teva '098 application.

**4.2. The Symed '478 Application is entitled to the benefit of its parent PCT application with respect to the Proposed Count**

The Symed '478 Application is a national stage filing of PCT/IN2003/00336 filed October 16, 2003. The disclosure of the parent application (PCT/IN2003/00336) is identical to that of the Symed '478 Application, a certified copy of the original PCT filing is attached as Exhibit C. Applicants accordingly submit that the Symed '478 Application is entitled to an effective filing date at least as early as the filing date of PCT/IN2003/00336, October 16, 2003.

Attached hereto as "Exhibit D" is a claim chart identifying support from the specification and drawings of the PCT/IN2003/00336 for each limitation recited in the Proposed Count. Because the specification of the Symed '478 Application supports each limitation of the Proposed Count, and the Symed '478 Application has an effective filing date at least as early as PCT/IN2003/00336, October 16, 2003, Exhibits C and D prove that Applicants are entitled to an earliest constructive reduction to practice date with respect to the Proposed Count of at least as early as October 16, 2003. As Applicants' October 16, 2003, earliest constructive reduction to practice date is earlier than the June 29, 2004, earliest constructive reduction to practice date with respect to the Teva '098 application (though U.S. Provisional Application No. 60/584,371), Applicants would prevail over Teva on priority.

In addition, because Applicants have shown, with respect to the Proposed Count, that Applicants have an earliest constructive reduction to practice date (based on the earliest effective filing dates of the Symed '478 Application) which predates the earliest constructive reduction to practice date for the subject matter claimed in the Teva '098 application (though U.S. Provisional Application No. 60/584,371), Applicants are the Senior Party in this requested interference as to the Proposed Count.

**4.3. The Symed '478 Application is entitled to senior party status whereas the Teva '098 application is entitled to junior party status**

The Symed '478 application is the senior party, and is entitled to the presumption under § 41.207(a)(1) that it is the prior inventor. As set forth, *supra*, Applicants have shown, with respect to the Proposed Count, that Applicants have an earliest constructive reduction to practice date (based on the earliest effective filing dates of the Symed '478 Application) which predates the earliest constructive reduction to practice date for the subject matter claimed in the Teva '098 application.

The Teva '098 Application can only show a constructive reduction to practice date (based on the earliest effective filing dates of the '098 application though U.S. Provisional Application No. 60/584,371), and is therefore entitled to junior party status.

**4.4. COMPLIANCE WITH 35 U.S.C. 135(b)**

According to 35 USC 135(b)(2):

> (2) A claim which is the same as, or for the same or substantially the same subject matter as, a claim of an application published under section 122(b) of this title may be made in an application filed after the application is published only if the claim is made before 1 year after the date on which the application is published.

Here, the Symed '478 application set forth:

> Claim 1.A crystalline linezolid form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.

which is "substantially the same subject matter" as at least claims 8-9 of the Teva '098 application, and therefore satisfies 35 U.S.C. 135(b).

**(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification**

As set forth, *supra*, the Symed '478 application contained a claim drawn to substantially the same subject matter as at least claims 8-9 of the Teva '098 application. However, Applicant

herein provides Exhibit E is a claim chart identifying support from the specification and drawings of the Symed '478 Application for each limitation recited in the claims of the Symed '478 Application (and thus further to the Proposed Count).

**(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter**

The claim chart of Exhibit F identifies support from the Specification and Drawings of the '478 application for the Proposed Count. The claim chart of Exhibit F accordingly evidences' a constructive reduction to practice by Applicants within the scope of the interfering subject matter (as defined by the Proposed Count) as of the October 16, 2003 effective filing date of the Symed '478 Application.

In addition, the claim chart of Exhibit D identifies support from the specification and drawings of the PCT Application for each limitation recited in certain ones (i.e., counts 1-2 and 4-6) of the Proposed Count. The claim chart of Exhibit D accordingly evidences a constructive reduction to practice by Applicants within the scope of the interfering subject matter (as defined by the Proposed Count) as of the October 16, 2003, filing date of the PCT Application.

* * *

In view of the foregoing presentation, Applicants respectfully request that an interference be declared between the Symed '478 Application and the Teva '098 Application, and that the Symed '478 Application be accorded senior part status.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

June 4, 2009

By_____
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Attorneys for Applicants

Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.

**Exhibit A**

# EXHIBIT A

| PROPOSED COUNT | '478 Application (SYMED APP) | '098 Application (TEVA APP) | WHY INTERFERENCE |
|---|---|---|---|
| **Proposed Count** | **Claim** | **Claim** | |
| A crystalline linezolid characterized by: | 1. A crystalline linezolid form III, characterized by | 8. Crystalline linezolid characterized by data selected from the group consisting of: | |
| (a) a powder X-ray diffraction pattern with peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 21.1, 22.2, 25.4, 27.7, and 28.4 ± 0.2 degree 2 theta; OR | an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees, and | a) a powder X-ray diffraction pattern with peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 21.1, 22.2, 25.4, 27.7, and 28.4 ± 0.2 degree 2 theta; | anticipation |
| | | | |
| (b) an FTIR spectrum with peaks at about 2817, 1335, 1229, 1200, and 662 cm-1, | Inherent Characteristic | b) an FTIR spectrum with peaks at about 2817, 1335, 1229, 1200, and 662 cm-1; and | anticipation |
| | | | |
| | | | |
| wherein there is at least a 99.8% enantiomeric excess of the linezolid form III. | wherein there is at least a 99.8% enantiomeric excess of the linezolid form III. | and having a content of less than 0.5% (w/w) of the R-enantiomer of linezolid. | anticipation |
| | | | |

**Exhibit B**

MEMBER INFORMATION

# India and the WTO

This page gathers key information on India's participation in the WTO. India has been a WTO member since 1 January 1995.

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Ministry of Commerce and Industry
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**Exhibit C**

ECTUAL PROPERTY
INDIA

सत्यमेव जयते

# GOVERNMENT OF INDIA
# PATENT OFFICE
## Ministry of Commerce and Industry
## Department of Industrial Policy and Promotion

is hereby certified that annexed here to is a true copy of **PCT Request, escription, Claims, Abstract** of the patent application as filed and detailed low:-

| | | |
|---|---|---|
| te of application | : | **16-10-2003** |
| plication No. | : | **PCT/IN2003/000336** |
| plicants | : | **M/s. Symed Labs Limited,**<br>**8-3-166/6 & 7, II Floor, Sree Arcade,**<br>**Erragadda, Hyderabad 500 018,**<br>**Andhra Pradesh, India.** |

In witness there of
I have here unto set my hand

Dated this the 8th day of May 2009
18th day of Vaisakha, 1931 (Saka)

By Authority of
THE CONTROLLER GENERAL OF PATENTS,
DESIGNS AND TRADE MARKS.

(V. RENGASAMY)
DEPUTY CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE
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| | | |
|---|---|---|
| 0-1 | For receiving Office use only<br>International Application No. | PCT/IN03/00336 |
| 0-2 | International Filing Date | 16 OCTOBER 2003 (16.10.03) |
| 0-3 | Name of receiving Office and "PCT International Application" | THE PATENT OFFICE, (INDIA)<br>PCT INTERNATIONAL APPLICATION |

| | | |
|---|---|---|
| 0-4 | Form - PCT/RO/101 PCT Request | |
| 0-4-1 | Prepared using | PCT-EASY Version 2.92<br>(updated 01.07.2003) |
| 0-5 | Petition<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| 0-6 | Receiving Office (specified by the applicant) | Indian Patent Office (RO/IN) |
| 0-7 | Applicant's or agent's file reference | SLL-PCT-1 |
| I | Title of invention | A NOVEL CRYSTALLINE FORM OF LINEZOLID |
| II | Applicant | |
| II-1 | This person is: | applicant only |
| II-2 | Applicant for | all designated States except US |
| II-4 | Name | SYMED LABS LIMITED |
| II-5 | Address: | 8-3-166/6&7, II Floor,<br>Sree Arcade<br>Erragadda, Hyderabad,<br>Andhrapradesh.<br>500 018 Hyderabad<br>India |
| II-6 | State of nationality | IN |
| II-7 | State of residence | IN |
| II-8 | Telephone No. | 0091-40-23812650 |
| II-9 | Facsimile No. | 0091-40-23708104 |
| II-10 | e-mail | dmohanrao@symedlabsltd.com |

REQUEST

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| | | |
|---|---|---|
| III-1 | Applicant and/or inventor | |
| III-1-1 | This person is: | applicant and inventor |
| III-1-2 | Applicant for | US only |
| III-1-4 | Name (LAST, First) | MOHAN RAO, dodda |
| III-1-5 | Address: | Symed Labs Limited,<br>8-3-166/6&7, II Floor, Sree Arcade,<br>Erragadda, Hyderabad,<br>Andhrapradesh.<br>500 018 Hyderabad<br>India |
| III-1-6 | State of nationality | IN |
| III-1-7 | State of residence | IN |
| III-2 | Applicant and/or inventor | |
| III-2-1 | This person is: | applicant and inventor |
| III-2-2 | Applicant for | US only |
| III-2-4 | Name (LAST, First) | KRISHNA REDDY, pingili |
| III-2-5 | Address: | Symed Labs Limited,<br>8-3-166/6&7, II Floor, Sree Arcade,<br>Erragadda, Hyderabad,<br>Andhrapradesh.<br>500 018 Hyderabad<br>India |
| III-2-6 | State of nationality | IN |
| III-2-7 | State of residence | IN |
| V | Designation of States | |
| V-1 | Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT<br>EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT<br>EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT<br>OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT |

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| | | |
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| 2 | National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned) | AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW |
| 5 | Precautionary Designation Statement<br>In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. | |
| | Exclusion(s) from precautionary designations | NONE |
| | Priority claim | NONE |
| 1 | International Searching Authority Chosen | Austrian Patent Office (ISA/AT) |
| | Declarations | Number of declarations |
| 1 | Declaration as to the identity of the inventor | - |
| 2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | 1 |
| 3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - |
| 4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | 1 |
| 5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - |

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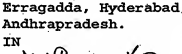
| VIII-2-1 | Declaration: Entitlement to apply for and be granted a patent<br>Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:<br>Name: | in relation to this international application<br><br>SYMED LABS LIMITED<br>is entitled to apply for and be granted a patent by virtue of the following: |
| VIII-2-1 (ii) | | SYMED LABS LIMITED is entitled as employer of the inventor, MOHAN RAO, dodda |
| VIII-2-1 (ii) | | SYMED LABS LIMITED is entitled as employer of the inventor, KRISHNA REDDY, pingili |
| VIII-2-1 (ix) | This declaration is made for the purposes of: | all designations except the designation of the United States of America |

| | | |
|---|---|---|
| VIII-4-1 | **Declaration: Inventorship (only for the purposes of the designation of the United States of America)**<br>Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America: | I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.<br>This declaration is directed to the international application of which it forms a part (if filing declaration with application).<br>I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.<br>I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed. |
| VIII-4-1-1 | Prior applications: | |

| | | |
|---|---|---|
| | | I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.<br>I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. |
| VIII-4-1 -1-1 | Name: | MOHAN RAO, dodda |
| VIII-4-1 -1-2 | Residence: (city and either US State, if applicable, or country) | Hyderabad, India |
| VIII-4-1 -1-3 | Mailing address: | Erragadda, Hyderabad, Andhrapradesh. |
| VIII-4-1 -1-4 | Citizenship: | IN |
| VIII-4-1 -1-5 | Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) |  |
| VIII-4-1 -1-6 | Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application) | 15\|10\|2003 |

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| | | |
|---|---|---|
| VIII-4-1 -2-1 | Name: | KRISHNA REDDY, pingili |
| VIII-4-1 -2-2 | Residence: (city and either US State, if applicable, or country) | Hyderabad, India |
| VIII-4-1 -2-3 | Mailing address: | Erragadda, Hyderabad, Andhrapradesh. |
| VIII-4-1 -2-4 | Citizenship: | IN |
| VIII-4-1 -2-5 | Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent) | P. Krishna Reddy |
| VIII-4-1 -2-6 | Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application) | 15/10/2003 |

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| | Check list | number of sheets | electronic file(s) attached |
|---|---|---|---|
| IX-1 | Request (including declaration sheets) | 8 | - |
| IX-2 | Description | 7 | - |
| IX-3 | Claims | 3 | - |
| IX-4 | Abstract | 1 | EZABST00.TXT |
| IX-5 | Drawings | 0 | - |
| IX-7 | TOTAL | 19 | |
| | **Accompanying items** | **paper document(s) attached** | **electronic file(s) attached** |
| IX-8 | Fee calculation sheet | ✓ | - |
| IX-17 | PCT-EASY diskette | - | Diskette |
| IX-19 | Figure of the drawings which should accompany the abstract | | |
| IX-20 | Language of filing of the international application | English | |
| X-1 | Signature of applicant, agent or common representative | | |
| X-1-1 | Name | SYMED LABS LIMITED | 15/10/2003 |
| X-1-2 | Name of signatory | MOHAN RAO, dodda | |
| X-2 | Signature of applicant, agent or common representative | | |
| X-2-1 | Name (LAST, First) | MOHAN RAO, dodda | 15/10/2003 |
| X-3 | Signature of applicant, agent or common representative | | |
| X-3-1 | Name (LAST, First) | KRISHNA REDDY, pingili | 15/10/2003 |

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| 10-1 | Date of actual receipt of the purported international application | 16 OCTOBER 2003 (16.10.03) |
| 10-2 | Drawings: | |
| 10-2-1 | Received | |
| 10-2-2 | Not received | |
| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
| 10-4 | Date of timely receipt of the required corrections under PCT Article 11(2) | |
| 10-5 | International Searching Authority | ISA/AT |
| 10-6 | Transmittal of search copy delayed until search fee is paid | |

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# PCT-EASY INFORMATION SHEET

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## VALIDATION LOG

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| Green? | Contents<br>The international application contains no drawings. Please verify. |
| Green? | Annotate<br>The name of the person signing the request or/and the capacity in which the person signs has/have not been indicated. Please be informed that some receiving Offices require that this information be present along with the signature. |

**Before submitting the International Application, please carefully verify that:**

**-the information contained on printed Request form is correct;**
**-Box X of the Request form has been signed;**
**-all elements of the international application as indicated in Boxes VIII and IX of the Request form have been attached; and,**
**-the diskette containing the PCT-EASY zip file of the International Application has been enclosed and has been clearly labeled "PCT-EASY", with the applicant's or agent's file reference, and the first applicant's name.**

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invention relates to a novel crystalline form of linezolid, to processes for its preparation and to a ical composition containing it.

ANNEX: FEE CALCULATION SHEET)

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| | | |
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| 0 | For receiving Office use only | |
| 0-1 | International Application No. | PCT/ IN03/00336 |
| 0-2 | Date stamp of the receiving Office | 16 OCTOBER 2003 (16.10.03) |

| | | | | | |
|---|---|---|---|---|---|
| 0-4 | Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet | | | | |
| 0-4-1 | Prepared using | | PCT-EASY Version 2.92 (updated 01.07.2003) | | |
| 0-9 | Applicant's or agent's file reference | | SLL-PCT-1 | | |
| 2 | Applicant | | SYMED LABS LIMITED, et al. | | |
| 12 | Calculation of prescribed fees | | fee amount/multiplier | Total amounts (USD) | Total amounts (INR) |
| 12-1 | Transmittal fee | T | ⇨ | | |
| 12-2-1 | Search fee | S | ⇨ | 183 | 0 |
| 12-2-2 | International search to be carried out by | | AT | | |
| 12-3 | International fee | | | | |
| | Basic fee (first 30 sheets) | b1 | 476 USD | | |
| 12-4 | Remaining sheets | | 0 | | |
| 12-5 | Additional amount | (X) | 12 USD | | |
| 12-6 | Total additional amount | b2 | 0 USD | | |
| 12-7 | b1 + b2 = | B | 476 USD | | |
| 12-8 | Designation fees | | | | |
| | Number of designations contained in international application | | 98 | | |
| 12-9 | Number of designation fees payable (maximum 5) | | 5 | | |
| 12-10 | Amount of designation fee | (X) | 104 USD | | |
| 12-11 | Total designation fees | D | 520 USD | | |
| 12-12 | PCT-EASY fee reduction | R | -148 USD | | |
| 12-13 | Total International fee (B+D-R) | I | ⇨ | 848 | |
| 12-17 | TOTAL FEES PAYABLE (T+S+I+P) | | ⇨ | 1,031 | |
| 12-19 | Mode of payment | | bank draft | | |

## VALIDATION LOG AND REMARKS

| | | |
|---|---|---|
| 13-2-7 | Validation messages Contents | Green? The international application contains no drawings. Please verify. |

T (ANNEX - FEE CALCULATION SHEET)
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| | | |
|---|---|---|
| 13-2-1<br>0 | Validation messages<br>Annotate | Green?<br>The name of the person signing the request or/and the capacity in which the person signs has/have not been indicated. Please be informed that some receiving Offices require that this information be present along with the signature. |

PCT/ I N03/00336

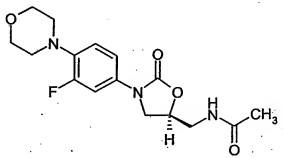
# A NOVEL CRYSTALLINE FORM OF LINEZOLID

## FIELD OF THE INVENTION

The present invention relates to a novel crystalline form of linezolid, to processes for its preparation and to a pharmaceutical composition containing it.

## BACKGROUND OF THE INVENTION

Linezolid, chemically N-[[(5S)-3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide is an antibacterial agent. Linezolid is represented by the following structure:



Linezolid and related compounds, processes for their preparation and their therapeutic uses were disclosed in US 5,688,792. Processes for preparation of linezolid were also described in US 5,837,870, WO 99/24393, J.Med.Chem. 39(3), 673-679, 1996 and Tetrahedron Lett., 40(26), 4855, 1999.

Linezolid is known to exhibit polymorphism and two crystalline forms are so far known. US 6,559,305 and US 6,444,813 addressed that the product obtained by the process described by J.Med.Chem. 39(3), 673-679, 1996 is form I and is characterized by having melting point of 181.5-182.5°C and by IR spectrum having bands at 3284, 3092, 1753, 1728, 1649, 1565, 1519, 1447, 1435 $cm^{-1}$. US 6,559,305 claims crystalline form II characterized by IR spectrum having bands at 3364, 1748, 1675, 1537, 1517, 1445, 1410, 1401, 1358, 1329, 1287, 1274, 1253, 1237, 1221, 1145, 1130, 1123, 1116, 1078, 1066, 1049, 907, 852 and 758 $cm^{-1}$ and powder X-ray diffraction spectrum having 2-theta values

at 7.10, 9.54, 13.88, 14.23, 16.18, 16.79, 17.69, 19.41, 19.69, 19.93, 21.61, 22.39, 22.84, 23.52, 24.16, 25.28, 26.66, 27.01 and 27.77 degrees.

We have discovered a novel crystalline form (form III) of linezolid. The novel crystalline form of linezolid is consistently reproducible, does not have the tendency to convert to other forms and found to be thermally more stable than form I or form II. Furthermore, form III bulk solid is more compact and less electrostatic than form II and hence is more readily subjected to any treatment under the usual conditions of the pharmaceutical technology, in particular, of formulation on an industrial scale. Therapeutic uses of linezolid were disclosed in US 5,688,792.

The object of the present invention is to provide a stable, consistently reproducible crystalline form of linezolid; processes for preparing it; and a pharmaceutical composition containing it.

## SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III.

Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.

Linezolid form III is further characterized by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 $cm^{-1}$.

Linezolid form III is obtained by heating linezolid in a known crystalline form or in a mixture of known crystalline forms until the known form/s are converted to form III.

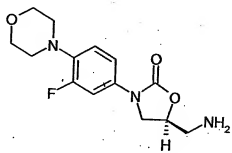
The known form may be heated directly to obtain linezolid form III; or linezolid form III may be obtained by heating linezolid suspended in a solvent like toluene, xylene, etc.

The conversion to form III occurs at above about 90°C, preferably between 100°C and 200°C and more preferably between 120°C and 140°C.

The heating takes at least about 30 min, usually about 2 hours to 12 hours and typically about 4 hours to 10 hours.

In accordance with the present invention, an alternative process is provided for preparation of linezolid form III, which comprises the steps of:

a) acetylating (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]amine of formula



in a solvent optionally in the presence of an organic base to form linezolid;

b) optionally seeding the reaction mixture formed in step (a); and

c) isolating linezolid form III from the reaction mixture of (a) or (b);

wherein the solvent is selected from the group consisting of ethylacetate, methylacetate, propylacetate, isopropylacetate, butylacetate, acetonitrile, chloroform, methylenedichloride, benzene, toluene and xylene.

The organic base is preferably selected from pyridine; tri(C1-C4)alkylamine e.g. triethylamine and N,N-diisopropyl ethylamine; and N.N-di(C1-C3)alkylaniline e.g. N,N-dimethylaniline.

In accordance with the present invention, still another process is provided for preparation of linezolid form III, which comprises the steps of:

a) mixing linezolid with a solvent or a mixture of solvents;

b) cooling the contents to below about 15$^0$C;

c) optionally seeding the contents with linezolid form III;

d) stirring the contents for at least about 15 min; and

e) collecting linezolid form III crystals by filtration or centrifugation;

wherein the solvent is selected from the group consisting of toluene, xylene, chloroform methylene dichloride, acetonitrile, water, $R_1$-OH, $R_1$-CO-$R_2$, $R_1$-CO-O-$R_2$, $R_1$-O-$R_2$ wherein $R_1$ and $R_2$ are independently $C_1$-$C_6$ alkyl groups. Preferable solvents are toluene, xylene, chloroform, methylene dichloride, acetonitrile, water, methanol, ethanol, propanol, isopropyl alcohol, tert-butyl

alcohol, acetone, methyl ethyl ketone, ethylacetate, diethyl ether and methyl tert-butyl ether. Most preferable solvents are isopropyl alcohol and ethylacetate.

In accordance with the present invention, there is provided a pharmaceutical composition comprising linezolid form III and a pharmaceutically acceptable carrier or diluent.

## DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III.

Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.

Linezolid form III is further characterized by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 $cm^{-1}$.

Linezolid form III is obtained by heating linezolid in a known crystalline form or in a mixture of known crystalline forms until the known form/s are converted to form III.

The known form may be heated directly to obtain linezolid form III; or linezolid form III may be obtained by heating linezolid suspended in a solvent like toluene, xylene, etc.

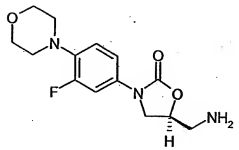
The conversion to form III occurs at above about 90°C, preferably between 100°C and 200°C and more preferably between 120°C and 140°C.

The heating takes at least about 30 min, usually about 2 hours to 12 hours and typically about 4 hours to 10 hours.

No recimization occurs during the heating of linezolid as evidenced by enantiomeric purity, which is same before and after heating.

In accordance with the present invention, an alternative process is provided for preparation of linezolid form III.

Thus, (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]amine of formula



is reacted with an acetylating agent, like acetic anhydride, acetyl chloride, in a solvent optionally in the presence of an organic base and linezolid formed is isolated from the reaction mixture.

The solvent is selected from the group consisting of ethylacetate, methylacetate, propylacetate, isopropylacetate, butylacetate, acetonitrile, chloroform, methylenedichloride, benzene, toluene and xylene.

The organic base is preferably selected from pyridine; tri(C1-C4)alkylamine e.g. triethylamine and N,N-diisopropyl ethylamine; and N.N-di(C1-C3)alkylaniline e.g. N,N-dimethylaniline.

Preferably, (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine is mixed in ethyl acetate, acetic anhydride is added maintaining the reaction temperature at or below boiling temperature of ethylacetate, preferably at about 15°C to 40°C; the reaction mixture is agitated preferably at about 15°C to 40°C for at least 15 min; and linezolid form III is collected by filtration or centrifugation.

The reaction mixture is optionally seeded with linezolid form III before isolating linezolid form III.

In accordance with the present invention, still another process is provided for preparation of linezolid form III.

Thus, linezolid is mixed with a solvent. Linezolid is preferably mixed at boiling point of the solvent used. The solvent is selected from the group consisting of toluene, xylene, chloroform methylene dichloride, acetonitrile, water, $R_1$-OH, $R_1$-CO-$R_2$, $R_1$-CO-O-$R_2$, $R_1$-O-$R_2$ wherein $R_1$ and $R_2$ are independently $C_1$-$C_6$ alkyl groups. Preferable solvents being toluene, xylene, chloroform, methylene dichloride, acetonitrile, water, methanol, ethanol, propanol, isopropyl alcohol, tert-butyl alcohol, acetone, methyl ethyl ketone,

ethylacetate, diethyl ether and methyl tert-butyl ether. Most preferable solvents being isopropyl alcohol and ethylacetate. A mixture of solvents may also be used and solvents like hexane, heptane may also be added in order to enhance crystallization in latter stages. Linezolid obtained by a known method is used in the process.

The solution obtained as above is cooled to below about 15°C, preferably to about 0°C to about 15°C, more preferably to about 0°C to about 10°C.

The contents are optionally seeded with linezolid form III.

The contents are then stirred for at least about 15 min, preferably for about 30 min to 8 hours and more preferably about 1 hour to about 5 hours.

Linezolid form III crystals are then collected by filtration or centrifugation.

In accordance with the present invention, there is provided a pharmaceutical composition comprising linezolid form III and a pharmaceutically acceptable carrier or diluent.

The invention will now be further described by the following examples; which are illustrative rather than limiting.

Example 1

Linezolid (10 gm, obtained by the process described in US 5,688,792 Example 5) is heated at 130°C to 140°C under $N_2$ atmosphere for 4 hours to give linezolid form III quantitatively.

Example 2

Linezolid form II (10 gm, with 99.8% ee) is suspended in toluene (50 ml) and refluxed for 3 hours. the contents are cooled to 25°C and filtered to obtain 9.8 gm of linezolid form III (99.8% ee).

Example 3

Linezolid (10 gm, obtained by the process described in US 5,688,792 Example 5) is mixed with isopropyl alcohol (200 ml), heated to 80°C and stirred for 10 min at the same temperature to form a clear solution. The solution is cooled to 0°C, stirred for 1 hour 30 min at 0°C and filtered to give 9.7 gm of linezolid form III

Example 4

Example 3 is repeated by seeding the solution with linezolid form III during maintenance at about 0°C. Yield of linezolid form III is 9.6 gm.

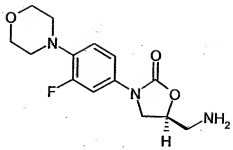
Example 5

To the mixture of (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]amine (10 gm) and ethylacetate (100 ml), acetic anhydride (10 ml) is slowly added at ambient temperature, then stirred at ambient temperature for 1 hour. The separated solid is filtered and dried under reduced pressure at 50°C to give 9.5 gm of linezolid form III.

We claim:

1. A crystalline linezolid form III, characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees.
2. A crystalline linezolid form III as defined in claim 1, further characterized by by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 $cm^{-1}$.
3. A process for preparation of linezolid form III as defined in claim 1, which comprises the step of heating linezolid in a known crystalline form or in a mixture of known crystalline forms until the known form/s are converted to form III.
4. A process according to claim 3, wherein linezolid is heated directly or linezolid suspended in a solvent is heated.
5. A process according to claim 4, wherein linezolid is heated at above about 90°C for at least 30 min.
6. A process according to claim 5, wherein linezolid is heated between 100°C and 200°C for about 2 hours to 12 hours.
7. A process according to claim 6, wherein linezolid is heated between 120°C and 140°C for about 4 hours to 10 hours.
8. A process according to claim 4, wherein linezolid suspended in toluene is heated at about boiling temperature of the solvent for about 4 hours to 10 hours.
9. A process according to claim 4, wherein linezolid suspended in xylene is heated at about boiling temperature of the solvent for about 4 hours to 10 hours.
10. A process for preparation of linezolid form III as defined in claim 1, which comprises the steps of:

a) acetylating (S)-N-[[3-[3-fluoro-4-[4-morpholinyl]phenyl]-2-oxo-5-oxazolidinyl] methyl]amine of formula in a solvent



optionally in the presence of an organic base to form linezolid;

b) optionally seeding the reaction mixture formed in step (a); and

c) isolating linezolid form III from the reaction mixture of (a) or (b);

wherein the solvent is selected from the group consisting of ethylacetate, methylacetate, propylacetate, isopropylacetate, butylacetate, acetonitrile, chloroform, methylenedichloride, benzene, toluene and xylene.

11. A process according to claim 10, wherein the process is carried out in the presence of the organic base.

12. A process according to claim 10, wherein the organic base is selected from pyridine, tri(C1-C4)alkylamine and N,N-di(C1-C3)alkylaniline.

13. A process according to claim 12, wherein the organic base is pyridine, triethylamine, N,N-diisopropyl ethylamine and N,N-dimethylaniline.

14. A process according to claim 10, wherein the process is carried out in the absence of the organic base.

15. A process according to claim 10-14, wherein the solvent is ethylacetate.

16. A process according to claim 10-15, wherein linezolid form III is isolated without seeding.

17. A process according to claim 10-15, wherein linezolid form III is isolated after seeding.

18. A process for preparation of linezolid form III as defined in claim 1, which comprises the steps of:

a) mixing linezolid with a solvent or a mixture of solvents;

b) cooling the contents to below about $15^0$C;

c) optionally seeding the contents with linezolid form III;

d) stirring the contents for at least about 15 min; and

e) collecting linezolid form III crystals by filtration or centrifugation;

wherein the solvent is selected from the group consisting of toluene, xylene, chloroform methylene dichloride, acetonitrile, water, $R_1$-OH, $R_1$-CO-$R_2$, $R_1$-CO-O-$R_2$ and $R_1$-O-$R_2$ where $R_1$ and $R_2$ are independently $C_1$ to $C_2$ alkyl groups.

19. A process according to claim 18, wherein the solvent is selected from toluene, xylene, chloroform, methylene dichloride, acetonitrile, water, methanol, ethanol, propanol, isopropyl alcohol, tert-butyl alcohol, acetone, methyl ethyl ketone, ethylacetate, diethyl ether and methyl tert-butyl ether.

20. A process according to claim 19, wherein the solvent is isopropyl alcohol or ethyl acetate.

21. A process according to claim 20, wherein the solvent is isopropyl alcohol.

22. A process according to claim 20, wherein the solvent is ethyl acetate.

23. A process according to claim 18, wherein the contents in step (b) is cooled to 0°C to 10°C and stirring the contents in step (d) for about 30 min to 8 hours;

24. A pharmaceutical composition comprising linezolid form III of claim 1 and a pharmaceutically acceptable carrier or diluent.

Abstract:

The present invention relates to a novel crystalline form of linezolid, to processes for its preparation and to a pharmaceutical composition containing it.

**Exhibit D**

## EXHIBIT D

| PROPOSED COUNT | SYMED - PCT APPLICATION SPECIFICATION SUPPORT |
|---|---|
| **Proposed Count** | |
| A crystalline linezolid characterized by: | In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III. (page 2, lines 16-17) |
| (a) a powder X-ray diffraction pattern with peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 21.1, 22.2, 25.4, 27.7, and 28.4 ± 0.2 degree 2 theta; OR | Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees. (page 2, lines 18-20) |
| | |
| (b) an FTIR spectrum with peaks at about 2817, 1335, 1229, 1200, and 662 cm-1, | Inherent Characteristic |
| wherein there is at least a 99.8% enantiomeric excess of the linezolid form III. | Example 2 (page 6, lines 22-25) discloses the conversion of linezolid form II into linezolid form III, with an enantiomeric excess of 99.8%. In addition, Example 3 (page 6, lines 26-31) discloses the conversion of linezolid to linezolid form III, with 97% enantiomeric excess, and Example 4 (page 6, lines 32-34) discloses linezolid form III with an enantiomeric excess of 96%. Additionally, Example 5 (page 7, lines 1-6) discloses linezolid form III with an enantiomeric excess of 95%. Thus the Specification supports the limitation "at least a 99.8% enantiomeric excess of the linezolid form III". |
| | |

**Exhibit E**

## EXHIBIT E

| '478 (SYMED) APPLICATION CLAIMS | '478 (SYMED) APPLICATION SPECIFICATION SUPPORT |
|---|---|
| 1. A crystalline linezolid form III, characterized by | In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III (page 2, lines 16-17). |
| an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees, and | Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees (page 2, lines 18-20). |
| and further characterized by an IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 $cm^{-1}$ | Linezolid form III is further characterized by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm-1 (page 2, lines 21-24). |
| wherein there is at least a 99.8% enantiomeric excess of the linezolid form III. | Example 2 (page 6, lines 22-25) discloses the conversion of linezolid form II into linezolid form III, with an enantiomeric excess of 99.8%. In addition, Example 3 (page 6, lines 26-31) discloses the conversion of linezolid to linezolid form III, with 97% enantiomeric excess, and Example 4 (page 6, lines 32-34) discloses linezolid form III with an enantiomeric excess of 96%. Additionally, Example 5 (page , lines 1-6) discloses linezolid form III with an enantiomeric excess of 95%. Thus the Specification supports the limitation "at least a 99.8% enantiomeric excess of linezolid form III". |
| | |
| 39. A crystalline linezolid form III, characterized by | In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III (page 2, lines 16-17). |

| | |
|---|---|
| an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees, and | Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees (page 2, lines 18-20). |
| and further characterized by an IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 $cm^{-1}$. | Linezolid form III is further characterized by IR spectrum having main bands at about 3338, 1741, 1662, 1544, 1517, 1471, 1452, 1425, 1400, 1381, 1334, 1273, 1255, 1228, 1213, 1197, 1176, 1116, 1082, 1051, 937, 923, 904, 869, 825 and 756 cm-1 (page 2, lines 21-24). |
| | |

**Exhibit F**

# EXHIBIT F

| PROPOSED COUNT | SYMED '478 APPLICATION SPECIFICATION SUPPORT |
|---|---|
| **Proposed Count** | |
| A crystalline linezolid characterized by: | In accordance with the present invention, there is provided a novel crystalline form of linezolid, designated as linezolid form III. (page 2, lines 16-17) |
| (a) a powder X-ray diffraction pattern with peaks at about 7.5, 13.5, 18.0, 18.7, 19.9, 21.1, 22.2, 25.4, 27.7, and 28.4 ± 0.2 degree 2 theta; OR | Linezolid form III is characterized by peaks in the powder x-ray diffraction spectrum having 2θ angle positions at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees. (page 2, lines 18-20) |
| | |
| (b) an FTIR spectrum with peaks at about 2817, 1335, 1229, 1200, and 662 cm-1, | Inherent Characteristic |
| wherein there is at least a 99.8% enantiomeric excess of the linezolid form III. | Example 2 (page 6, lines 22-25) discloses the conversion of linezolid form II into linezolid form III, with an enantiomeric excess of 99.8%. In addition, Example 3 (page 6, lines 26-31) discloses the conversion of linezolid to linezolid form III, with 97% enantiomeric excess, and Example 4 (page 6, lines 32-34) discloses linezolid form III with an enantiomeric excess of 96%. Additionally, Example 5 (page 7, lines 1-6) discloses linezolid form III with an enantiomeric excess of 95%. Thus the Specification supports the limitation "at least a 99.8% enantiomeric excess of the linezolid form III". |
| | |